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10/581,656	06/09/2008	Hyung-Joo Kwon	BARUN-10974	3937

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EXAMINER	
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ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,656	KWON ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☒ Claim(s) *3-7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 April 2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7 are pending in the application and under examination.

Sequence Requirements

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § § 1.821-1.825 for the reason(s) set forth below. Full compliance with the sequence rules is required in response to this office action.

The specification discloses sequences on p. 12 line 23, p. 13 lines 1-3, line19, p. 18 line 9, lines 11-12, 14-15, p. 21 line 10, p. 22 lines 22-23 and figures 3, and 6 disclose sequences encompassed by the definitions for nucleotide sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). These sequences are not identified by the requisite sequence identification # i.e. SEQ ID NO:.

Drawings

The drawings in this application are objected due to sequence compliance issues. Figures 3, and 6 disclose sequences encompassed by the definitions for nucleotide sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). These sequences are not identified by the requisite sequence identification # i.e. SEQ ID NO:.

Specification

The disclosure is objected to because of the following informalities: on p. 31 line 5 there is a word missing between 'every five' and 'during 2 weeks'.

Appropriate correction is required.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Information Disclosure Statement

The information disclosure statement filed 12/22/08 has been considered. An initialed copy is enclosed.

Election/Restrictions

Applicant's election of the species SEQ ID NO: 3 in Paper No. 20081115 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Objections

Claims 3-7 are objected to because of the following informalities:

'any of the claims 1 and 2' – should be 'any one of claims 1 and 2'. Appropriate correction is required. See MPEP 608.01(n).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claimed invention is drawn to a product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Additionally, purity of naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui 156 USPQ 426 (1966). However when purity results in new utility, patentability is considered. Merck Co. V. Chase Chemical Co. 273 F. Supp 68 (1967). See also American Wood v. Fiber Disintegrating Co., 90 US 566 (1974);American Fruit Growers v. Brogdex Co. 283 US 1 (1931); Funk Brothers Seed Co. V. Kalo Innoculant Co. 33 US 127 (1948). In the instant case the oligonucleotides are based on nucleic acid sequences of Mycobacterium bovis. *Amendment to the claims to recite the essential purity* (e.g. purify or isolated) and thus reflect the hand of man in the claimed products is suggested to obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to oligodeoxynucleotides for stimulating an adjuvant or treating immune-related diseases or for protecting normal immune cells when radiotherapy is applied or for treating or preventing skin diseases, presented in General Formula:[General Formula]: HKCGTTCRTGTCSGM (SEQ ID NO: 1)wherein, R represents A or G; S represents C or G; H represents A, T or C; K represents G or T; and M represents C or A and oligodeoxynucleotides for stimulating an adjuvant or treating immune-related diseases according to the claim 1,wherein the oligonucleotides further comprise five nucleotides, presented in following General Formula, at a 5'-terminal end and a 3'-terminal end:[General Formula]: DKMHKCGTTCRTGTCSGMYK (SEQ ID NO: 2)wherein, R represents

A or G; S represents C or G; H represents A, T or C; K represents G or T; D represents A, G or T; M represents C or A; M represents C or A; and Y represents C or T.

The claims are drawn to a genus of CpG motif containing oligonucleotides encompassed by the formula set forth in SEQ ID NO: 1 or SEQ ID NO: 2. The species of oligonucleotides have the properties of 1) treating immune related diseases (2) adjuvant 3) protect normal immune cells when radiotherapy is applied 4) treat or prevent skin diseases and 5) balance various Th1/Th2 immune reactions.

The specification discloses SEQ ID NO: 3 (aka MB-ODN 4/5#31) that induces inflammatory cytokine production. Other oligonucleotides were found to activate Il-18 or Il-12 promoters of macrophages. Thus, the oligonucleotides have immune stimulating activity albeit some more than others and could be used as adjuvants.

However, out of the genus of oligonucleotides disclosed only one species SEQ ID NO: 3 was reduced to practice for treating atopic dermatitis in an animal model by suppressing expression of cytokine mediated by Th2 to reduce IgE level in the serum while increasing expressing of Th1 cytokines and for protecting normal immune cells when radiotherapy is applied. See p. 30 example 7 and p. 34 example 8.

The specification does not reduce to practice any other oligonucleotide encompassed by the instant generic formulas with treating immune related diseases, treating and preventing skin diseases, or protecting immune cells from radiotherapy

The genus of oligonucleotides is described by structure but there is no correlation with treating immune related diseases, treating and preventing skin diseases, or protecting immune cells from radiotherapy.

Oligonucleotides comprising CpG motifs were known in the art and the immune responses to such oligonucleotides is well characterized (See Uhlmann et al. Current Opinion in Drug Discovery & Development 2003 6(2):204-217, cited in IDS). However, the art teaches that the CpG motif containing oligonucleotides are not equivalent in their ability to generate immune responses i.e. some are more optimal than others, also as to their use in therapy, different CpG motifs were optimal in two different models of cancer (See Ballas et al. The Journal of Immunology, 2001, 167:4878-4886, p. 4878 column 2 last paragraph, p. 4879 table 1 CpG ODN with distinct immune profiles). Ballas et al teaches that CpG ODN 1585 was optimal against B16 melanoma and required NK cells while CpG ODN 1826 was optimal in another lymphoma model and its effects appeared to require NK and T cells (see p. 4878 column 2 last paragraph). Ballas et al also shows that treatment or prevention of B16 melanoma (a type of skin cancer) in an animal with CpG motif containing oligonucleotides (ODN) varies with type of CpG ODN used and a host of other factors. For treatment of established tumors, the factors included the number of tumors administered, the type of CpG ODN, dose of the CpG and the frequency of the doses (see Ballas et al p. 4880 fig. 1 and column 1 and fig. 2). For protection against melanoma challenge i.e. prevention, not all CpG ODN tested were equally effective and even one type of CpG – CpG2006 was not effective since it had results

similar to the non-CpG control ODN (Ballas et al p. 4881 column 1 and fig. 4). Thus, the art clearly teaches that even though CpG ODN stimulate immune responses uses for treatment and prevention of immune related diseases including skin cancer is complex and efficacy depends on many factors and one cannot predict efficacy of one CpG ODN based on efficacy on a structurally different CpG ODN even though they possess the immune stimulating CpG motif.

In the instant case, the description of one species of oligonucleotide (SEQ ID NO: 3) that treats atopic dermatitis, protecting normal immune cells when radiotherapy is applied is insufficient to describe the large and variant genus of oligonucleotides claimed that treats any immune related disease, any skin disease or prevents any skin disease and protects normal immune cells when radiotherapy is applied. In such an unpredictable art, as set forth supra, adequate written description of a genus (with the instant functional properties) which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See *Noelle v Lederman*. 355 F. 3d 1343, 1350, 69 USPQ2d 1508, 1514 (*Fed. Cir. 2004*) and *In re Alonso* (Fed. Cir. 2008-1079). Even , though the genus of oligonucleotides comprise a common structure that is CpG or a CpG motif, the art clearly teaches that all CpG motif containing oligonucleotides are not equivalent especially when it comes to therapy or prevention. Applicants were in possession of the instant genus of oligonucleotides which were found to activate Il-18 or Il-12 promoters of

macrophages (fig. 4 and 5) and thus have immune stimulating activity (albeit some more than others) and could be used as adjuvants.

However, Applicants were as of the time of filing *not* in the possession of the instant genus of oligonucleotides which 1) treats immune related diseases 2) protect normal immune cells when radiotherapy is applied 3) treat or prevent skin diseases and 5) balance various Th1/Th2 immune reactions but were in possession of SEQ ID NO: 3 which 1) treats atopic dermatitis, protects normal immune cells when radiotherapy is applied and increases Th1 cytokines while suppressing Th2 cytokines.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the instant oligonucleotides with generic formula SEQ ID NO: 1 or SEQ ID NO: 2 for use as adjuvant and enabling for SEQ ID NO: 3 for treating atopic dermatitis and the use of SEQ ID NO: 3 for protecting normal immune cells when radiotherapy is applied, does not reasonably provide enablement for the instant use of the other oligonucleotides with generic formula SEQ ID NO: 1 or SEQ ID NO: 2 for treating other immune related diseases or other skin diseases or for preventing skin diseases or for protecting normal immune cells when radiotherapy is applied. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to oligodeoxynucleotides for stimulating an adjuvant or treating immune-related diseases, presented in General Formula:[General Formula]:

HKCGTTCRTGTCSGM (SEQ ID NO: 1)wherein, R represents A or G; S represents C or G; H represents A, T or C; K represents G or T; and M represents C or A and oligodeoxynucleotides for stimulating an adjuvant or treating immune-related diseases according to the claim 1,wherein the oligonucleotides further comprise five nucleotides, presented in following General Formula, at a 5'-terminal end and a 3'-terminal end:[General Formula]: DKMHKCGTTCRTGTCSGMYK (SEQ ID NO: 2)wherein, R represents A or G; S represents C or G; H represents A, T or C; K represents G or T; D represents A, G or T; M represents C or A; M represents C or A; and Y represents C or T. Embodiments of the above formula is set forth in claim 7.

The intended use of the instant CpG motif containing oligonucleotides is as an adjuvant or for treating any immune related disorder or for treating and preventing any type of skin diseases.

The use of the instant oligonucleotides is very broad i.e. for treating a plethora of immune related disorders or treating or preventing skin diseases in general. There are many types of immune related disorders such as severe combined immunodeficiency syndrome, cell mediated immunity deficiency syndromes, X-linked agammaglobulinaemia, antibody deficiency syndrome (see Herbet et al, The Dictionary of Immunology, page 89). Other immune related diseases include AIDS, cancers, atopic dermatitis, asthma, allergies and the plethora of other diseases wherein the ability of the immune system to function properly is impaired or where the immune system itself is the culprit. Skin disease include skin cancer, allergic dermatitis, acne, pigmentation, melanoma, psoriasis, eczema, ringworm, chickenpox, rosacea, scars, scleroderma etc to name a few.

The specification teaches that at least 71 oligonucleotides activate the immune system to produce cytokines (see fig.4) The specification also correlates the immune response generated by O-type MB-ODN4/5#31 (aka SEQ ID NO: 3) oligonucleotides with treatment of atopic dermatitis in an animal model (see fig. 12). The specification, however, does not correlate the immune response generated with treatment of other types of immune related diseases such as AIDS, cancers, atopic dermatitis, asthma, allergies, severe combined immunodeficiency syndrome, cell mediated immunity deficiency syndromes, X-linked agammaglobulinaemia, antibody deficiency syndrome or treatment or prevention of any type of skin diseases known in the art including but not limited to skin cancer, allergic dermatitis, acne, pigmentation, melanoma, psoriasis, eczema, ringworm, chickenpox, rosacea, scars, scleroderma etc to name a few. Taking skin cancer for example, treatment of cancer in general is very complex and there are many types and furthermore the specification does not provide guidance as to whether the instant oligonucleotides can act like a 'vaccine' to prevent feature skin cancer or any other type of a skin related disease. Ability of the instant oligonucleotides to induce an immune response is not provided with a correlation with treating any immune related disease or treating and preventing any skin disease. The specification at the time of filing does not correlate the immune responses generated with treatment of AIDS even in an animal model. Thus, for an immune system deficiency such as AIDS for which the pathogenesis is unclear, it is unpredictable that the instant oligonucleotide can treat or prevent AIDS. The instant specification does not correlate the immune responses generated by the instant oligonucleotide with treatment or prevention of AIDS due to HIV.

Oligonucleotides comprising CpG motifs were known in the art and the immune responses to such oligonucleotides is well characterized (See Uhlmann et al. Current Opinion in Drug Discovery & Development 2003 6(2):204-217, cited in IDS). However, the art teaches that the CpG motif containing oligonucleotides are not equivalent in their ability to generate immune responses i.e. some are more optimal than others, also as to their use in therapy, different CpG motifs were optimal in two different models of cancer (See Ballas et al. The Journal of Immunology, 2001, 167:4878-4886, p. 4878 column 2 last paragraph, p. 4879 table 1 CpG ODN with distinct immune profiles). Ballas et al teaches that CpG ODN 1585 was optimal against B16 melanoma and required NK cells while CpG ODN 1826 was optimal in another lymphoma model and its effects appeared to require NK and T cells (see p. 4878 column 2 last paragraph). Ballas et al also shows that treatment or prevention of B16 melanoma (a type of skin cancer) in an animal with CpG motif containing oligonucleotides (ODN) varies with type of CpG ODN used and a host of other factors. For treatment of established tumors, the factors included the number of tumors administered, the type of CpG ODN, dose of the CpG and the frequency of the doses (see Ballas et al p. 4880 fig. 1 and column 1 and fig. 2). For protection against melanoma challenge i.e. prevention, not all CpG ODN tested were equally effective and even one type of CpG – CpG2006 was not effective since it had results similar to the non-CpG control ODN (Ballas et al p. 4881 column 1 and fig. 4). Thus, the art clearly teaches that even though CpG ODN stimulate immune responses uses for treatment and prevention of immune related diseases including skin cancer is complex and efficacy depends on many factors and one cannot predict efficacy of one CpG ODN based on efficacy on a structurally different CpG ODN even though they possess the immune stimulating CpG motif. The instant specification teaches that

CpG motif containing ODN i.e. MB-ODN4/5#31 or SEQ ID NO: 3 when applied as ointment 0.2mg /head to Atopic dermatitis lesion on mice 4 times resulted in disappearance of the skin lesions compared to un-treatment group and protected normal immune cells when radiotherapy was applied. See fig. 12 and p. 30-31. The specification is devoid of guidance as to how to use SEQ ID NO: 3 or other disclosed ODN's to treat other immune related diseases or treat or prevent other skin diseases – i.e. the dose, frequency, which particular CpG ODN, route of administration which are important factors for therapy with CpG ODN. Also, because of these factors the effects of SEQ ID NO: 3 in treatment of other immune related diseases or treating or preventing skin diseases or for protecting normal immune cells when radiotherapy is applied is unpredictable. In addition, the efficacy of other CpG oligonucleotides encompassed by the instant generic formulas for treating atopic dermatitis cannot be predicted from the efficacy of SEQ ID NO: 3 in treating atopic dermatitis in the mouse because as evidenced by fig. 5 and 6, the ODNS have differing effects on the immune system. Thus, while the oligonucleotides encompassed by the generic formulas may reasonably be used as adjuvants, when it comes to treatment of an immune related disease or skin disease or for protecting normal immune cells when radiotherapy is applied the specification is only enabling for SEQ ID NO:3 for treatment of atopic dermatitis and for protecting normal immune cells when radiotherapy is applied. Also, the specification is not enabling for the other oligonucleotides encompassed by the generic formulas formula for preventing any skin disease ,other immune related diseases and protecting normal immune cells when radiotherapy is applied and undue experimentation would be required of the skilled artisan to use the invention commensurate with the scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 1, how do the oligonucleotides stimulate an adjuvant? Do Applicants mean that the oligonucleotides are used as adjuvant?

Claim 3 recites the limitation "when the radiotherapy is applied. There is insufficient antecedent basis for this limitation in the claim or in the preceding claims..

In claim 5, the metes and bounds of "balances various Th1/Th2 immune reactions' is not clear in the claim. Specifically, the metes and bounds of 'balances' is not clear. In what way does the oligonucleotides balance the Th1/Th2 immune reaction? It is not clear whether a TH1 immune reaction is increased or decreased and whether a Th2 immune reaction is increased or decreased and from what baseline level.

As to claim 2, the claim recites that the oligonucleotides of claim 1 further comprise 5 nucleotides at a 5'terminal and a 3' terminal. However, SEQ ID NO: 2 does not have 5 additional nucleotides at the 3' terminal but only two nucleotides

Status of Claims

Claims 1-7 are rejected. Claims 3-7 are objected to. No claimed allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to OLUWATOSIN OGUNBIYI whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am- 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Oluwatosin Ogunbiyi/
Examiner, Art Unit 1645

/Robert B Mondesi/
Supervisory Patent Examiner,
Art Unit 1645